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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,682	12/14/2005	Takaki Koga	14875-147US1 C1-A0226P-US	5413

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,682	KOGA ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7 and 13-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,6,7,13 and 15-21* is/are allowed.

6)☐ Claim(s) *3,5,14 and 22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received February 28, 2008 are acknowledged.

Claims 4 and 8-12 have been canceled.
Claims 1-3, 5-7, 13, and 14 have been amended.
Claims 15-30 have been added.

Claims 1-10, 13, and 14 are under examinations as they read on antibodies, compositions, and kits comprising anti-PCI antibodies.

Specification

2. Applicant's amendments to the specification are noted.

Information Disclosure Statement

3. Applicant's IDS form received 12/04/07 is acknowledged and has been considered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 1-3, 5-7, 13, and 14 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement have been withdrawn in view of applicant's claim amendments received 2/28/08 which address all the issues raised in the rejection of record.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. The rejection of claims 1-3 and 5 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter has been withdrawn in view of applicant's claim amendments received 2/28/08 which recite that the claimed antibodies have been isolated, thus demonstrating the hand of man in the instant claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 3 and 23-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Meijers et al (of record) as evidenced by Elisen et al. (of record) for the reasons of record.

The office action mailed September 28, 2007 states:

> Meijers et al. disclose monoclonal antibodies that bind protein C inhibitor (PCI) and inhibit the ability of PCI to inactivate activated protein C (aPC) in purified systems and in plasma (see entire document, particularly the abstract). These antibodies are disclosed as being present in a composition comprising Tris buffer, a known pharmaceutically acceptable carrier (see particularly the right column of page 1401).
>
> Additionally, given that the antibodies of Meijers et al. comprise the recited functional activities, given that antibodies PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6 also comprise these activities, and given that the functional properties of antibody binding to an antigen are determined by the antigen epitope that is bound by the antibody, the antibodies of Meijers et al. and antibodies PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6 compete for the same antibody-binding site because the functional consequences of antibody binding are the same. Further, given that the antibodies of Meijers et al. comprise the recited biological activities, the antibodies of Meijers et al. are "functionally equivalent" to the antibodies that are recited by SEQ ID number in claim 4.
>
> It is noted that Meijers et al. did not test their antibody for blocking interactions of PCI with thrombin/thrombomodulin. However, the instant specification discloses that the binding sites on PCI for aPC and thrombin overlap (see particularly page 13) and Meijers et al. disclose that their antibody inhibited PCI in plasma which comprises thrombin and thrombomodulin. Further, the prior art of Elisen et al. discloses that the major function of PCI in plasma during coagulation is

the inhibition of thrombin (see entire document, particularly the abstract). Given that clotting activity increases in the assays of Meijers et al. subsequent to antibody administration in plasma, the prior art disclosure of Elisen et al. that the major role of PCI in plasma is to inhibit thrombin, and the facts that aPC dissolves clots whereas thrombin generates clots, the anti-PCI antibodies of Meijers et al. must also inhibit interactions between PCI and thrombin based upon the reported experimental data of Meijers et al. As per MPEP 2112, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Therefore, the prior art anticipates the claimed invention.

Applicant's arguments filed February 28, 2008 have been fully considered but they are not persuasive. Applicant argues that Meijers et al. disclose no sequence data and that therefore the instant claims cannot be anticipated.

This argument is not persuasive because of the reasons set forth in the rejection of record. Note that the claimed antibodies do not comprise any of the recited sequence information. Since the claimed antibodies and the antibodies of Meijer et al. comprise the same functional properties upon antigen binding, in the absence of evidence to the contrary, the claimed and prior art antibodies bind the same or overlapping epitopes and thus "compete" for antigen binding. Applicant is reminded that as per MPEP 2145, "Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration."

Applicant also argues that antibodies can bind to multiple epitopes to cause the same functional result, and thus there is no evidence that the prior art antibodies bind the same epitopes as the claimed antibodies.

This argument is not persuasive. The claims in question do not recite that the antibodies bind "the same" epitopes, but instead recite that there is competition for binding. As such, antibodies can bind epitopes which are not "the same" but yet compete due to phenomena including steric hindrance and conformational changes in the antigen. Further, applicant's arguments that not all PCI antibodies have all of the recited functional activities is not persuasive since claim 3 states "inhibition of one or both of" and thus applicant has argued limitations not claimed. As was stated supra, given the same biological activity, in the absence of evidence to the contrary, it is reasonable that the prior art and claimed antibodies "compete" and attorney arguments do not substitute for evidence where evidence is required.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 3 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijers et al (of record) in view of Kovari et al. (Structure, 1995, 3:1291-3) for the reasons of record.

The office action mailed September 28, 2007 states:.

> The disclosure of Meijers et al. has been discussed above, and differs form the instant claimed invention in that they do not disclose antibody fragments.

> Kovari et al. disclose that antibody fragments are useful in obtaining crystals for structure determination studies because binding of antibody fragments, such as Fab, to the target antigen can effectively transform aggregated material into a soluble, monodisperse sample suitable for crystallization and that some proteins can only be crystallized when present in a complex comprising an antibody fragment (see entire document, particularly the left column of page 1291). They further disclose that solving the x-ray diffraction pattern of the resultant crystal is aided by the fact that the antibody fragment can be used for molecular replacement or as a recipient of heavy atom labels (see particularly the right column of page 1292).
>
> Therefore, a person of ordinary skill in the art would have been motivated at the time the invention was made to make well known antibody fragments, such as Fab, from the antibodies disclosed by Meijers et al. so that the antibody fragments could be used in methods of determining the three dimensional structure of PCI using the methods disclosed by Kovari et al.

Applicant's arguments filed February 28, 2008 have been fully considered but they are not persuasive. Applicant argues that the prior art antibodies do not comprise the recited sequences and thus cannot form the basis for an obviousness rejection.

This argument is not persuasive since the claimed antibodies "compete" with antibodies that have the recited sequences yet the antibodies being claimed do not actually comprise said sequences. Thus applicant is arguing limitations not claimed.

12. The following are new rejections necessitated by applicant's claim amendments received 2/28/08.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 5, 14, 22, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites human antibodies and depends from claim 1 which has been amended to recite CDR sequences obtained from mouse monoclonals. The claim also recites humanized antibodies. Given that the CDRs of the claimed antibodies are of mouse origin, the claimed antibodies cannot be "human". Further, applicant cannot intend human to mean “CDR grafting into human frameworks and constant region”

since "humanized" is also recited. As such it is unclear what applicant means by the recitation of "human".

Claims 14 and 30 recite a kit comprising "at least one of PC, aPC, and an antibody" and as such only one of these three molecules is required. However, part (b) of the claim recites printed materials that refer to the use of these components in combination. Since the components are not required to be present in combination in part (a), the claim is logically inconsistent and thus is indefinite.

Claim 22 is indefinite because there is no sequence in the specification disclosed as SEQ ID NO:4,4. Does this recitation mean SEQ ID NO:4, SEQ ID NO:44, or something entirely different? Appropriate amendment is required.

15. Claims 14 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Grinnell et al., US Patent 6,037,322.

Grinnell et al. disclose kits comprising activated protein C and printed directions (see entire document, particularly the paragraph spanning columns 3 and 4). Note that the claims recite "a kit comprising at least one of PC, aPC and an antibody" and thus only one of the three molecules is required to be present in the claimed kit.

Thus the prior art anticipates the claimed invention.

16. Claims 3 and 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinnell et al. (US 6,037,322) in view of Griffin et al. (WO 93/09807) in view of Meijers et al. (of record).

Grinnell et al. disclose kits comprising activated protein C (aPC) and instructions which are use to treat thrombosis (see entire document, particularly the abstract, claims and the paragraph spanning columns 3 and 4). This disclosure differs from the claimed invention in that the kits are not disclosed as further comprising antibodies that bind protein C inhibitor (PCI).

Griffen et al. disclose the use of agents which upon administration to a patient increase circulation levels of endogenous aPC to treat thrombosis and

thromboembolisms (see entire document, particularly the abstract and page 6). Particular disclosed agents include specific antibodies against PC inhibitors, with inhibitors of PCI specifically contemplated (see particularly pages 7 and 12). Such agents are further disclosed as being administered in conjunction with aPC itself (see particularly page 28).

Meijers et al. disclose monoclonal antibodies that bind protein C inhibitor (PCI) and inhibit the ability of PCI to inactivate activated protein C (aPC) in purified systems and in plasma (see entire document, particularly the abstract).

Therefore it would have been obvious to a person or ordinary skill in the art at the time the invention was made to combine aPC and anti-PCI antibodies into compositions and kits. Motivation to do so comes from the disclosure of Griffen et al. that aPC and PCI inhibitors, such as specific antibodies against PC inhibitors, are to be combined for use in treating thrombotic disorders. A person or ordinary skill in the art would have been further motivated to include the monoclonal anti-PCI antibodies of Meijers et al in such compositions and kits because their antibodies have been demonstrated to inhibit the ability of PCI to inactivate aPC in plasma.

It is noted that the epitope specificity, other than that they bind PCI, of the antibodies of Meijers et al. is not reported. However, given that the functional properties that arise from antibody binding, such as activation, inhibition, etc..., are dependent upon the precise epitope bound, and that the recited and prior art antibodies both inhibit PCI inactivation of aPC, the property of binding "competing" epitopes arises intrinsically from maintenance of function. Further note that the antibodies present in the claimed compositions and kits are not required to comprise any of the sequence information recited in the instant claims.

Additionally, it should be noted that the "recording medium" recited in part (b) of claim 30 does not alter the structure of the claimed kit and that as per MPEP 2112.01, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, **>367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004)< (Claim at issue was a kit requiring

instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.)

17. Claims 1, 2, 6, 7, 13, 15-21 are allowable.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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